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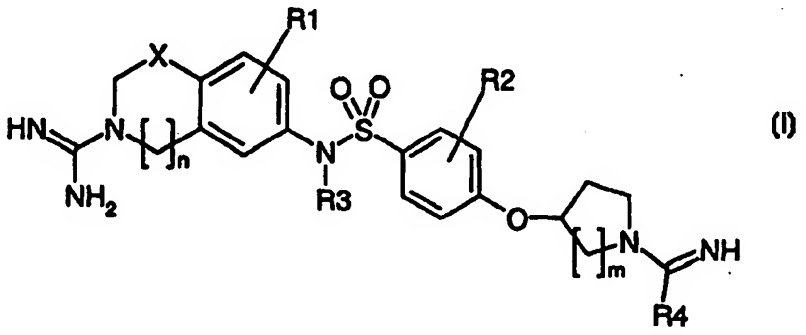

(I)

(57) Abstract

The invention relates to novel sulphonamides of general formula (I) in which R^1 to R^4 have the meaning indicated, and their hydrates, solvates and physiologically tolerable salts, optically active forms, racemates and diastereomer mixtures, processes for their preparation and medicaments which contain these compounds, for the treatment of thromboembolic disorders.

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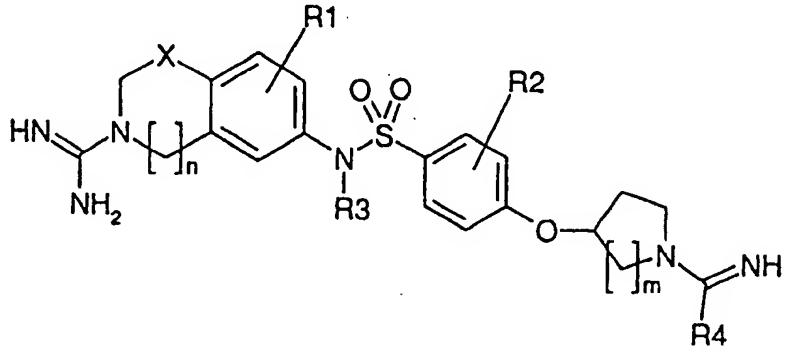
SULFONAMIDES WITH ANTITHROMBOTIC ACTIVITY

The invention relates to novel sulphonamides of the general formula I



(I)

in which

R^1, R^2 independently of one another can be a hydrogen atom, a halogen atom, a hydroxyl group, an alkyl group, a cycloalkyl group, an alkenyl group, an alkynyl group, an aryl radical, a heteroaryl radical, an alkoxy group, an aralkyloxy group, an alkenyloxy group, an alkynyloxy group, a carboxyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a hydroxyalkyl group, an alkoxyalkyl group, a carboxyalkyl group, an alkyloxycarbonylalkyl group, an alkenyloxycarbonylalkyl group or an alkynyloxycarbonylalkyl group;

R^3 can be a hydrogen atom, an alkyl group, a cycloalkyl group, an alkenyl group, an alkynyl group, an aralkyl radical, a hydroxyalkyl group, an alkoxyalkyl group, an aminoalkyl group, a carboxyalkyl group, an alkyloxycarbonylalkyl group, an alkenyloxycarbonylalkyl group or an

alkynyloxycarbonylalkyl group, an alkylcarbonyl radical, an arylcarbonyl group, a carboxyalkylsulphonyl group, an alkyloxycarbonylalkylsulphonyl group, a dihydroxyborylalkyl group, a dialkoxyborylalkyl group or an optionally substituted 1,3,2-dioxaborolanylalkyl group or an optionally substituted 1,3,2-dioxaborinanylalkyl group;

R^4 is an optionally substituted amino group, an alkyl group, a cycloalkyl radical, an optionally substituted aryl radical or an optionally substituted heteroaryl radical;

X is a single bond, a carbonyl group, or an alkylene or an alkylenoxy group;

n is the number 1 or 2 and

m is an integer between 1 and 4,

and hydrates, solvates and physiologically tolerable salts thereof. The invention also relates to the optically active forms, the racemates and the diastereomer mixtures of these compounds.

The invention also relates to processes for the preparation of the above compounds, medicaments which contain such compounds, and the use of these compounds in the production of medicaments, preferably those with antithromboembolic activity.

Moreover, the invention relates to a method for the prevention and treatment of diseases such as thrombosis, apoplexy, cardiac infarct, inflammations and arteriosclerosis, which comprises the administration of an effective amount of a compound of the formula I.

Further, the invention also relates to pharmaceutical preparations containing at least one

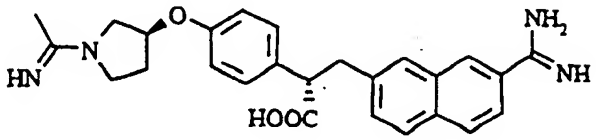
compound of the formula I besides conventional carriers and adjuvants.

The sulphonamides of the general formula I, their solvates and their salts intervene by means of reversible inhibition of factor Xa in the process of blood clotting and thus prevent the formation of hyaline thrombi. They can therefore be used in the control and prevention of diseases, such as thrombosis, apoplexy, cardiac infarct, inflammations and arteriosclerosis.

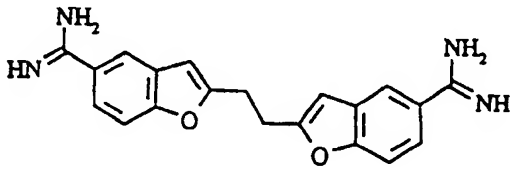
Factor Xa is a serine protease of the clotting system, which catalyses the proteolytic conversion of prothrombin into thrombin. Thrombin, as the last enzyme in the clotting cascade, on the one hand cleaves fibrinogen to fibrin, which after crosslinking by means of factor XIIIa becomes an insoluble gel and forms the matrix for a thrombus, and on the other hand, by proteolysis of its receptor on the blood platelets, activates platelet aggregation and in this way likewise contributes to thrombus formation. On injury of a blood vessel, these processes are necessary to stop bleeding. Under normal circumstances, measurable thrombin concentrations are not present in the blood plasma. An increase in the thrombin concentration can lead to the formation of thrombi and thus to thromboembolic diseases, which occur very frequently, especially in the industrial nations. As a result of the inhibition of factor Xa, the formation of thrombin can be prevented.

It has recently been reported that amidinoaryl-propanoic acid derivatives such as (+)-(2S)-2-[4-[[(3S)-1-acetimidoyl-3-pyrrolidinyl]oxy]phenyl]-3-(7-amidino-2-naphthyl)propanoic acid hydrochloride pentahydrate (DX-9065a; formula IIa) inhibits factor Xa (*J. Med. Chem.* **1994**, *37*, 1200-1207; *Thrombosis and Haemostasis* **1994**, *71*, 314-319; EP-0-540-051-A-1). Further known factor Xa inhibitors are 1,2-bis(5-amidino-2-benzofuranyl)ethane (DABE, formula IIb, *Thrombosis Research* **1980**, *19*, 339-349) or alternatively

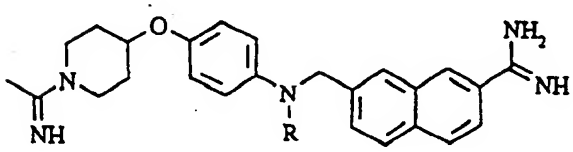
phenylaminomethylnaphthamidines of the general formula IIc (WO96/16940).



(IIa)



(IIb)



(IIc)

The novel sulphonamides of the general formula I according to the invention and hydrates, solvates and physiologically tolerable salts thereof are potent and selective factor Xa inhibitors.

In the general formula I, the substituents R^1 and R^2 can be identical or different.

If R^1, R^2 in the general formula I is a halogen atom, this can in each case be a fluorine, chlorine, bromine or iodine atom, but fluorine, chlorine or bromine substituents are preferred.

If R^1, R^2, R^3, R^4 in the general formula I is an alkyl group, this can be straight-chain or branched and can contain 1 to 8 carbon atoms. The methyl, ethyl, *n*-propyl, *i*-propyl, *n*-butyl, *i*-butyl, *t*-butyl, pentyl and the hexyl group are preferred.

If R^1, R^2, R^3, R^4 in the general formula I is a cycloalkyl group, this can be substituted or unsubstituted and can contain 3 to 8 carbon atoms. The cyclopropyl, cyclopentyl, cyclohexyl and the cyclooctyl group are preferred.

If R^1, R^2, R^3 in the general formula I is an alkenyl group, this can be straight-chain or branched and can contain 2 to 8 carbon atoms. The vinyl,

1-propenyl, 2-propenyl, 2-methyl-2-propenyl, 1-butenyl, 1-pentenyl and the 1-hexenyl group are preferred.

If R^1, R^2 in the general formula I is an alkynyl group, this can be straight-chain or branched and can contain 2 to 8 carbon atoms. The ethynyl and propargyl group are preferred.

If R^1, R^2, R^4 in the general formula I is an aryl radical, this is understood as meaning the phenyl, a biphenyl or a naphthyl group. The aryl radical can be unsubstituted or can optionally carry one or more C_1-C_8-alkyl substituents, preferably methyl, one or more C_1-C_8-alkyloxy substituents, preferably methoxy, one or more carboxyl groups, one or more C_1-C_8-alkoxycarbonyl substituents, preferably methoxycarbonyl or ethoxycarbonyl, or one or more halogen substituents. The specification C_1-C_8 here in each case stands for a straight-chain or branched alkyl chain having 1 to 8 carbon atoms. Halogens as substituents of the aryl radical can be fluorine, chlorine, bromine and iodine atoms, but preferably fluorine, chlorine or bromine atoms.

If R^1, R^2, R^3 in the general formula I is a heteroaryl radical, this is understood as meaning a thiophenyl, a benzothiophenyl, a furanyl, a benzofuranyl, a quinolinyl or an isoquinolinyl radical. The heteroaryl radical can be unsubstituted or can optionally carry one or more C_1-C_8-alkyl substituents, preferably methyl, one or more C_1-C_8-alkyloxy substituents, preferably methoxy, one or more carboxyl groups, one or more C_1-C_8-alkoxycarbonyl substituents, preferably methoxycarbonyl or ethoxycarbonyl, or one or more halogen substituents. The specification C_1-C_8 here in each case stands for a straight-chain or branched alkyl chain having 1 to 8 carbon atoms. Halogens as substituents of the heteroaryl radical can be fluorine, chlorine, bromine and iodine atoms, but preferably fluorine, chlorine or bromine atoms.

Alkoxy groups as substituents R^1, R^2 in the general formula I contain 1 to 8 carbon atoms and are

straight-chain or branched. The methoxy, ethoxy, *n*-propyloxy, *i*-propyloxy, *n*-butyloxy, *i*-butyloxy, *tert*-butyloxy, pentyloxy and the hexyloxy group are preferred.

If R^1, R^2 in the general formula I is an aralkyloxy group, this contains a phenyl group linked to a straight-chain or branched C_1-C_8-alkyl chain, a naphthyl group linked to a straight-chain or branched C_1-C_8-alkyl chain or a biphenyl group linked to a straight-chain or branched C_1-C_8-alkyl chain. The benzyloxy group, the p-phenylbenzyloxy group and the naphthylmethyloxy group are preferred here.

Alkenyloxy groups as substituents R^1, R^2 in the general formula I contain 3 to 8 carbon atoms and are straight-chain or branched. The vinyloxy and allyloxy group are preferred.

Alkynyloxy groups as substituents R^1, R^2 in the general formula I contain 3 to 8 carbon atoms and are straight-chain or branched. The propargyloxy group is preferred.

Alkoxycarbonyl groups as substituents R^1, R^2 in the general formula I contain straight-chain or branched alkyl chains having 1 to 8 carbon atoms. The methoxycarbonyl and the ethoxycarbonyl group and also the *i*-propyloxycarbonyl and the *tert*-butyloxycarbonyl group are preferred.

If R^1, R^2 in the general formula I is an alkenyloxycarbonyl group, this contains straight-chain or branched alkenyls having 3 to 8 carbon atoms. The allyloxycarbonyl group is preferred.

If R^1, R^2 in the general formula I is an alkynyloxycarbonyl group, this contains straight-chain or branched alkynyls having 3 to 8 carbon atoms. The proparyloxycarbonyl group is preferred.

If R^1, R^2 in the general formula I is a hydroxyalkyl group, this can be straight-chain or branched and can contain 1 to 8 carbon atoms. The hydroxymethyl, hydroxyethyl, hydroxypropyl,

hydroxybutyl, hydroxypentyl and the hydroxyhexyl group are preferred.

If R^1, R^2, R^3 in the general formula I is an alkoxyalkyl group, the alkyl radicals concerned are in each case to be understood as meaning straight-chain or branched alkyl chains having 1 to 8 carbon atoms. The methoxymethyl, ethoxymethyl, methoxyethyl and the ethoxyethyl group are preferred.

Carboxyalkyl groups as substituents R^1, R^2 in the general formula I contain alkyl groups having 1 to 8 carbon atoms and are straight-chain or branched. The carboxymethyl, the carboxyethyl and the carboxypropyl group are preferred.

If R^1, R^2, R^3 in the general formula I is an alkyloxycarbonylalkyl group, the alkyl radicals are in each case to be understood as meaning straight-chain or branched alkyl chains having 1 to 8 carbon atoms. The methoxycarbonylmethyl, ethoxycarbonylmethyl, methoxycarbonylethyl, ethoxycarbonylethyl, methoxycarbonylpropyl and the ethoxycarbonylpropyl group are preferred.

If R^1, R^2, R^3 in the general formula I is an alkenyloxycarbonylalkyl group, the alkenyl radicals are straight-chain or branched having 3 to 8 carbon atoms and the alkyl groups are straight-chain or branched having 1 to 8 carbon atoms. The allyloxycarbonylmethyl, allyloxycarbonylethyl and the allyloxycarbonylpropyl group are preferred.

If R^1, R^2, R^3 in the general formula I is an alkynyloxycarbonylalkyl group, the alkynyl radicals are straight-chain or branched having 3 to 8 carbon atoms and the alkyl groups are straight-chain or branched having 1 to 8 carbon atoms. The propargyloxycarbonylmethyl, propargyloxycarbonylethyl and the propargyloxycarbonylpropyl group are preferred.

If R^3 in the general formula I is an alkynyl group, this can be straight-chain or branched and can contain 3 to 8 carbon atoms. The propargyl group is preferred.

An aralkyl radical as a substituent R^3 in the general formula I is understood as meaning a phenyl group linked to a straight-chain or branched C_1-C_8-alkyl chain, a naphthyl group linked to a straight-chain or branched C_1-C_8-alkyl chain or a biphenyl group linked to a straight-chain or branched C_1-C_8-alkyl chain. The benzyl group, the p-phenylbenzyl group and the naphthylmethyl group are preferred here.

If R^3 in the general formula I is a hydroxyalkyl group, this can be straight-chain or branched and can contain 2 to 8 carbon atoms. The hydroxyethyl, hydroxypropyl, hydroxybutyl, hydroxypentyl and the hydroxyhexyl group are preferred.

If R^3 in the general formula I is an aminoalkyl group, this can be straight-chain or branched and can contain 2 to 8 carbon atoms. The aminoethyl, aminopropyl, aminobutyl, aminopentyl and the aminohexyl group are preferred.

A carboxyalkyl group as a substituent R^3 in the general formula I contains an alkyl chain having 1 to 8 carbon atoms and is straight-chain or branched. The carboxymethyl, the carboxyethyl and the carboxypropyl group are preferred.

If R^3 in the general formula I is an alkylcarbonyl radical, the alkyl group can be straight-chain or branched and can contain 1 to 8 carbon atoms. The acetyl and the propionyl group are preferred.

As an aryl fragment, an arylcarbonyl group as a radical R^3 in the general formula I contains a phenyl, a biphenyl or optionally a naphthyl group, but preferably a phenyl group. The aryl radical can be unsubstituted or can optionally carry one or more C_1-C_8-alkyl substituents, preferably methyl, one or more C_1-C_8-alkyloxy substituents, preferably methoxy, one or more carboxyl groups, one or more C_1-C_8-alkoxycarbonyl substituents, preferably methoxycarbonyl or ethoxycarbonyl, or one or more halogen substituents. The specification C_1-C_8 here in each case stands for a straight-chain or branched alkyl chain having 1 to 8

carbon atoms. Halogens as substituents of the aryl radical can be fluorine, chlorine, bromine and iodine atoms, but preferably fluorine, chlorine or bromine atoms.

If R^3 in the general formula I is a carboxyalkylsulphonyl group, this contains an alkyl chain having 1 to 8 carbon atoms, which is straight-chain or alternatively can be branched. The carboxymethylsulphonyl, the carboxyethylsulphonyl and the carboxypropylsulphonyl group are preferred.

If R^3 in the general formula I is an alkyloxycarbonylalkylsulphonyl group, the alkyl radicals are in each case to be understood as meaning straight-chain or branched alkyl chains having 1 to 8 carbon atoms. The methoxycarbonylmethylsulphonyl, ethoxycarbonylmethylsulphonyl, methoxycarbonylethylsulphonyl, ethoxycarbonylethylsulphonyl, methoxycarbonylpropylsulphonyl and the ethoxycarbonylpropylsulphonyl group are preferred.

If R^3 in the general formula I is a dihydroxyborylalkyl group, this contains a straight-chain or branched alkyl chain having 1 to 8 carbon atoms. The dihydroxyborylmethyl and the dihydroxyborylpropyl group are preferred.

If R^3 in the general formula I is a dialkoxyborylalkyl group, the respective alkyl radicals can independently of one another be straight-chain or branched and can contain 1 to 8 carbon atoms. The dimethoxyborylmethyl and the dimethoxyborylpropyl group are preferred.

If R^3 in the general formula I is a 1,3,2-dioxaborolanylalkyl group, the alkyl radical can be straight-chain or branched and can contain 1 to 8 carbon atoms. If appropriate, the 1,3,2-dioxaborolanyl radical can be substituted in the 4- and 5-position, namely by up to four methyl groups. The 1,3,2-dioxaborolanylmethyl group and the 4,4,5,5-tetramethyl-1,3,2-dioxaborolanylmethyl group are preferred.

If R^4 in the general formula I is an amino group, this can be unsubstituted or alternatively substituted, namely by one or two C_1-C_8-alkyl groups, preferably methyl or ethyl, by one or two C_3-C_8-cycloalkyl groups, preferably cyclopropyl, cyclopentyl, cyclohexyl or cyclooctyl, by one or two C_2-C_8-hydroxyalkyl groups, preferably hydroxyethyl or hydroxypropyl, by one or two C_3-C_8-alkenyl groups, preferably allyl, by one or two C_3-C_8-alkynyl groups, preferably propargyl, or by one or two aralkyl groups, preferably benzyl. The specification C_1-C_8-alkyl refers here to a straight-chain or branched alkyl chain having 1 to 8 carbon atoms. C_3-C_8-cycloalkyl refers here to a branched or unbranched cycloalkyl group having 3 to 8 carbon atoms. C_2-C_8-Hydroxyalkyl refers here to a straight-chain or branched alkyl chain having 2 to 8 carbon atoms, which can be substituted by one or more hydroxyl groups. C_3-C_8-Alkenyl here denotes a straight-chain or branched unsaturated chain of 3 to 8 carbon atoms. C_3-C_8-Alkynyl here denotes a straight-chain or branched chain of 3 to 8 carbon atoms. Aralkyl here denotes a phenyl group linked to a straight-chain or branched C_1-C_8-alkyl chain, a naphthyl group linked to a straight-chain or branched C_1-C_8-alkyl chain or a biphenyl group linked to a straight-chain or branched C_1-C_8-alkyl chain.

If X in the general formula I is an alkylene group, this can be straight-chain or branched and can contain 1 to 8 carbon atoms. The methylene group and the ethylene group are preferred.

If X in the general formula I is an alkylenoxy group, this can be straight-chain or branched and can contain 1 to 8 carbon atoms. The methylenoxy fragment is preferred.

Particularly preferred compounds of the general formula I are those in which

R^1, R^2 are identical or different and are a hydrogen atom, a fluorine atom, a chlorine atom, a hydroxyl group, a methyl group, an ethyl group,

a methoxy group, a benzyloxy group, an allyloxy group, a carboxyl group, a methoxy- or ethoxy-carbonyl group, a hydroxymethyl or hydroxyethyl group or a carboxymethyl group;

R^3 is a hydrogen atom, a methyl group, an ethyl group, an isopropyl group, a cyclopropyl group, a cyclohexyl group, an allyl group, a propargyl group, a benzyl group, a hydroxyethyl group, a hydroxypropyl group, a methoxyethyl group, an aminoethyl group, a carboxymethyl group, a carboxyethyl group, a carboxypropyl group, an ethoxycarbonylmethyl group, an ethoxycarbonyl-ethyl group, an ethoxycarbonylpropyl group, an acetyl group, a 4-methoxybenzoyl group, a carboxymethylsulphonyl group, a carboxyethyl-sulphonyl group, a carboxypropylsulphonyl group, an ethoxycarbonylmethylsulphonyl group, an ethoxycarbonylethylsulphonyl group, an ethoxycarbonylpropylsulphonyl group, a dihydroxyborylmethyl group, a dihydroxyboryl-propyl group, a 4,4,5,5-tetramethyl-1,3,2-dioxaborolanylmethyl group;

R^4 is an amino group, a methyl group, an ethyl group, a cyclopropyl group, a cyclohexyl group, a 4-methoxyphenyl group or a thienyl group;

X is a methylene group;

n is the number 1 and

m can be the number 1 or the number 2.

Particularly preferred compounds are also those in which R^1, R^2 and R^3 are hydrogen, R^4 is the group NH_2, X is the methylene group, n is the number 1 and m is the number 2.

The physiologically tolerable salts of the general formula I are understood as meaning, for example, formates, acetates, caproates, oleates, lactates or salts of carboxylic acids having up to 18 carbon atoms or salts of dicarboxylic acids and tricarboxylic acids such as citrates, malonates and tartrates or alkanesulphonates having up to 10 carbon atoms or p-toluenesulphonates or salicylates or trifluoro-acetates or salts of physiologically tolerable mineral acids such as hydrochloric acid, hydrobromic acid, hydriodic acid, sulphuric acid, phosphoric acid. The compounds of the formula I having one or two free acid groups on the phosphonate fragment can also form salts with physiologically tolerable bases. Examples of such salts are alkali metal, alkaline earth metal, ammonium and alkylammonium salts, such as the sodium, potassium, calcium or tetramethylammonium salt.

The compounds of the formula (I) can be solvated, in particular hydrated. Hydration can be carried out in the course of the preparation or can occur gradually as a result of hygroscopic properties of an initially anhydrous compound of the formula I.

The invention also relates to the optically active forms, the racemates and the diastereomer mixtures of compounds of the general formula I.

For the production of medicaments, the substances of the general formula I are mixed with suitable pharmaceutical carrier substances, aromatic substances, flavourings and colourants and are shaped, for example, as tablets or coated tablets or are suspended or dissolved in water or oil, e.g. in olive oil, with addition of appropriate auxiliaries.

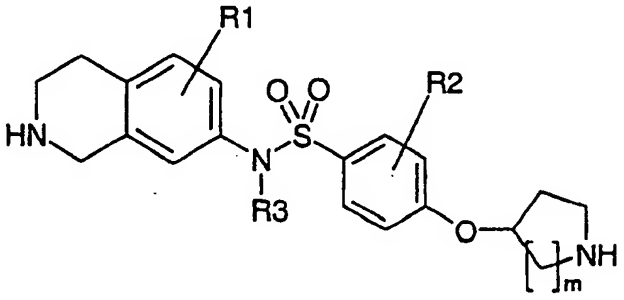
The substances of the general formula I and their salts can be administered orally, enterally or parenterally in liquid or solid form. The oral administration form is preferred. The injection medium used is preferably water, which contains the additives customary in injection solutions such as stabilizing agents, solubilizers or buffers. Additives of this type

are, for example, tartrate and citrate buffers, complexing agents (such as ethylenediaminetetraacetic acid and its non-toxic salts) and high molecular weight polymers such as liquid polyethylene oxide for viscosity regulation. Solid excipients are, for example, starch, lactose, mannitol, methylcellulose, talc, highly disperse silicic acids, high molecular weight fatty acids (such as stearic acid), animal and vegetable fats and solid high molecular weight polymers (such as polyethylene glycols). If desired, preparations suitable for oral administration can contain flavourings and sweeteners.

The compounds are customarily administered in amounts of 1-1500 mg per day based on a body weight of 75 kg. It is preferred to administer 1-2 tablets having an active compound content of 1-500 mg 2-3 times per day. The tablets can also be delayed release, as a result of which only 1-2 tablets containing 2-700 mg of active compound have to be given once per day. The active compound can also be given by injection 1-8 times per day or by continuous infusion, 5-2000 mg per day normally being sufficient.

Compounds of the general formula I are prepared by methods known per se.

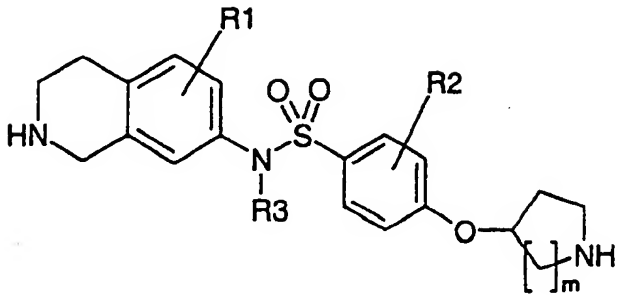
The compounds of the general formula I are prepared, for example, by reacting a compound of the general formula III



(III)

in which R^1, R^2, R^3 and m have the meanings indicated above, with a guanylating reagent in an inert solvent in the presence of an auxiliary base.

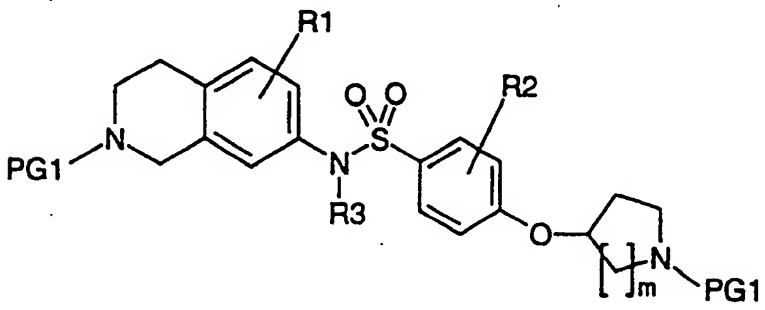
In detail, the compounds of formula I can be prepared, for example, by reacting a compound of the general formula III



(III)

in which R^1, R^2, R^3 and m have the meanings given above, with a guanylating reagent such as, for example, S-alkylisothiourea, preferably S-methylisothiourea, or 1H-pyrazole-1-carboxamidine (see e.g.: M.S. Bernatowicz, Y. Wu, G.R. Matseuda, J. Org. Chem. **1992**, 57, 2497-2505) in an inert solvent such as e.g. dimethylformamide, dioxan, dimethyl sulphoxide or toluene at temperatures between 0°C and the boiling point of the solvent, preferably at 0 to 30°C in the presence of an auxiliary base such as e.g. triethylamine, N-methylmorpholine, pyridine or ethyldiisopropylamine.

The compounds of the general formula III are prepared by reacting a compound of the general formula IV

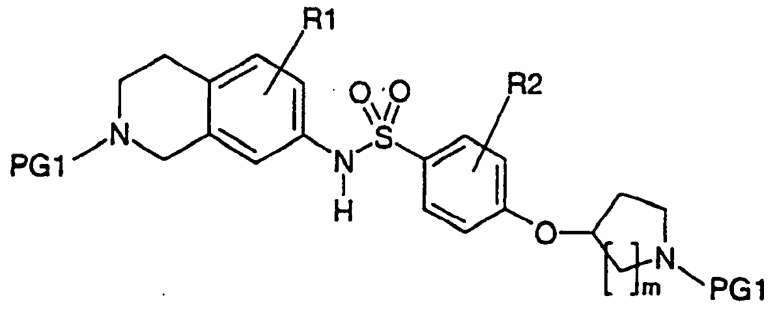


(IV)

in which R^1, R^2, R^3 and m have the meanings indicated above and PG^1 is a protective group such as, for example, the benzyloxycarbonyl group, the t-butyloxy-carbonyl group or the allyloxycarbonyl group, with a

reagent removing the protective group. The protective group removal is carried out according to generally customary methods (see, for example, T.W. Green, P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley and Sons Inc. 1991) by means of acidic reagents such as, for example, hydrogen bromide in glacial acetic acid or trifluoroacetic acid or ethereal HCl solution or hydrogenolytically or by means of palladium- or rhodium-catalysed cleavage.

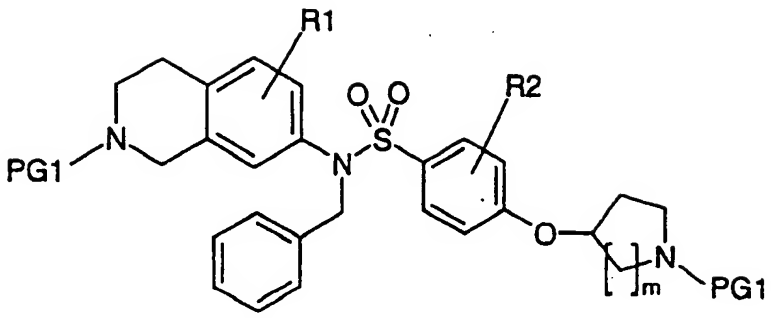
The compounds of the general formula IV are prepared by reacting a compound of the general formula V



(V)

in which R^1, R^2, PG^1 and m have the meanings indicated above, with compounds of the type R^3-Y, in which R^3 has the meaning indicated above and Y is halogen, tosylate, mesylate or triflate, in an inert solvent such as dioxane, tetrahydrofuran, N,N-dimethylformamide, N-methylpyrrolidone or toluene in the presence of a base such as, for example, sodium carbonate, potassium carbonate, 1,5-diazabicyclo[5.4.0]undec-5-ene or ethyl-diisopropylamine at temperatures between 0°C and the boiling point of the solvent, preferably between room temperature and 80°C. Compounds of the type R^3-Y are either commercially available or are known from the literature or can be prepared according to standard methods from precursors which are commercially available or are known from the literature.

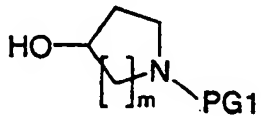
The compounds of the general formula V are prepared by subjecting a compound of the general formula VI



(VI)

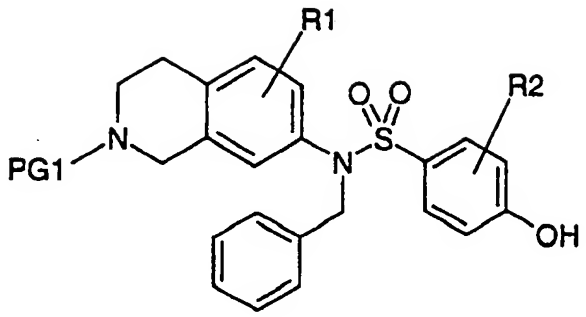
in which R^1, R^2, PG^1 and m have the meanings indicated above, to a catalytic hydrogenation in inert solvents such as, for example, methanol, ethanol, tetrahydrofuran or dioxane in the presence of a catalyst, preferably palladium on carbon. The benzyl group is replaced here by a hydrogen atom. The removal of the benzyl group is also carried out by reaction with a strong acid such as trifluoroacetic acid in the presence of mesitylene, anisole or thioanisole at temperatures between 0 and 50°C, preferably at room temperature, or by treatment with Lewis acids such as BF_3 etherate in an inert solvent such as toluene, acetonitrile, diethyl ether or tetrahydrofuran at temperatures between 0°C and the boiling point of the solvent, preferably between room temperature and the boiling point of the solvent.

The compounds of the general formula VI are prepared by condensing a compound of the general formula VII



(VII)

in which PG^1 and m have the meanings indicated above, with a compound of the general formula VIII

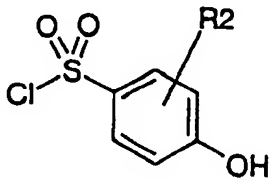


(VIII)

in which R^1, R^2 and PG^1 have the meanings indicated above, in an inert solvent such as dioxane, tetrahydrofuran or toluene in the presence of diethyl azodicarboxylate and triphenylphosphine, trimethyl or triethyl phosphite at temperatures between 0 and 50°C, preferably at room temperature.

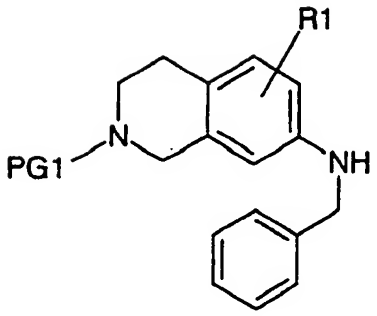
Compounds of the general formula VII in which m and PG^1 have the meanings indicated above are either commercially available or are known from the literature or can be prepared according to processes which are known from the literature (see, for example, K.L. Bhat, D.M. Flanagan, M.M. Jouillé, *Synth. Commun.* **1985**, *15*, 587-598; P.G. Houghton, G.R. Humphrey, D.J. Kennedy, D.C. Roberts, S.H. Wright, *J. Chem. Soc. Perkin Trans. 1* **1993**, *13*, 1421-1424; T.W. Green, P.G.M. Wuts "Protective Groups in Organic Synthesis", 2nd ed., John Wiley and Sons Inc. 1991).

The compounds of the general formula VIII are prepared by reacting a compound of the general formula IX



(IX)

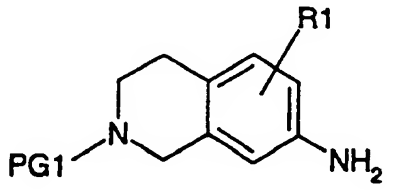
in which R^2 has the meaning indicated above, with a compound of the general formula X



(X)

in which R^1 and PG^1 have the meanings indicated above, in an inert solvent such as N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran, dichloromethane or toluene in the presence of a base such as, for example, sodium carbonate, potassium carbonate, 1,5-diazabicyclo[5.4.0]undec-5-ene, triethylamine, N-methylmorpholine or ethyldiisopropylamine at temperatures between -20°C and the boiling point of the solvent, preferably between 0°C and 80°C. Compounds of the type IX are either commercially available or are known from the literature or can be prepared according to standard methods from precursors which are commercially available or are known from the literature (see, for example, M. Sato, Y. Kawashima, J. Goto, Y. Yamane, Y. Chiba et al., *Eur. J. Med. Chem. Chim. Ther.* **1995**, *30*, 403-414; W. Loewe, T. Braden, *Arch. Pharm. (Weinheim Ger.)* **1995**, *328*, 283-286; R. Cremlin, F. Swinbourne, J. Atherall, L. Courtney, T. Cronje et al. *Phosphorus Sulphur* **1980**, *9*, 155-164; R.W. Campbell, H.W. Hill, *J. Org. Chem.* **1973**, *38*, 1047, Stewart *J. Chem. Soc.* **1922**, *121*, 2559).

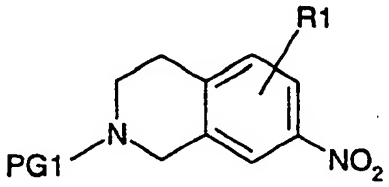
The compounds of the general formula X are prepared by reacting a compound of the general formula XI



(XI)

in which R^1 and PG^1 have the meanings indicated above, in an inert solvent such as dichloroethane, tetrahydrofuran, dioxane, ethanol, methanol or diglyme, in the presence of a reducing agent such as, for example, sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride, at temperatures between -20°C and the boiling point of the solvent, preferably between 0°C and 60°C.

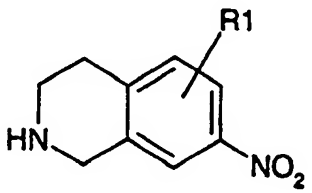
The compounds of the general formula XI are prepared by hydrogenating a compound of the general formula XII



(XII)

in which R^1 and PG^1 have the meanings indicated above, in an inert solvent such as methanol, ethanol, tetrahydrofuran or dioxane in the presence of a catalyst, for example palladium on carbon, tris-triphenylphosphine-rhodium chloride or Raney nickel. If appropriate, the reduction can also be carried out using reducing agents other than hydrogen, e.g. using lithium aluminium hydride, sodium borohydride/cobalt dichloride, sodium borohydride/nickel dichloride, triethylsilane/tris-triphenylphosphine-rhodium chloride or using base metals such as iron or tin in the presence of acid.

The compounds of the general formula XII are prepared by reacting a compound of the general formula XIII



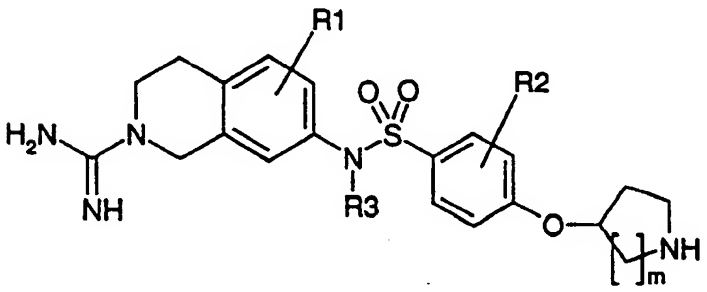
(XIII)

in which R^1 has the meaning indicated above, in an inert solvent such as methanol, ethanol, tetrahydrofuran, dioxane, dimethylformamide or water at tempera-

tures between 0°C and the boiling point of the solvent, preferably between room temperature and 50°C, with the appropriate commerically available reagents introducing the protective group, such as, for example, di-tert-butyl dicarbonate or chloroformic acid esters. The introduction of the appropriate protective group is carried out according to the generally known methods of protective group chemistry (see, for example, T.W. Green, P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley and Sons Inc. 1991), the presence of bases such as alkali metal or alkaline earth metal hydroxides, sodium carbonate, potassium carbonate, N-methylmorpholine, diisopropylethylamine, triethylamine or 1,5-diazabicyclo[5.4.0]undec-5-ene optionally being necessary.

Compounds of the type XIII are either commercially available or are known from the literature or can be prepared according to standard methods from precursors which are commercially available or are known from the literature (see, for example, J.F. Ajao, C.W. Bird, *J. Heterocycl. Chem.* **1985**, *22*, 329-331; E. Ochai, T. Nakagomo *Chem. Pharm. Bull.* **1958**, *6*, 497; A. McCoubrey, D.W. Mathieson, *J. Chem. Soc.* **1951**, 2851).

Compounds of the general formula I can also be prepared by reacting, for example, a compound of the general formula XIV

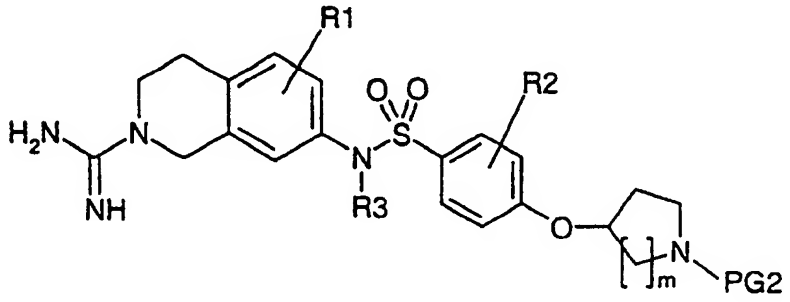


(XIV)

in which R^1, R^2, R^3 and m have the meanings indicated above, with aliphatic or aromatic imidate ester hydrochlorides in an inert solvent such as tetrahydrofuran, diethyl ether, ethanol, dimethylform-

amide or dioxane at temperatures between -20°C and the boiling point of the solvent, preferably between 0°C and 40°C, in the presence of an auxiliary base such as triethylamine, diisopropylethylamine or N-methylmorpholine.

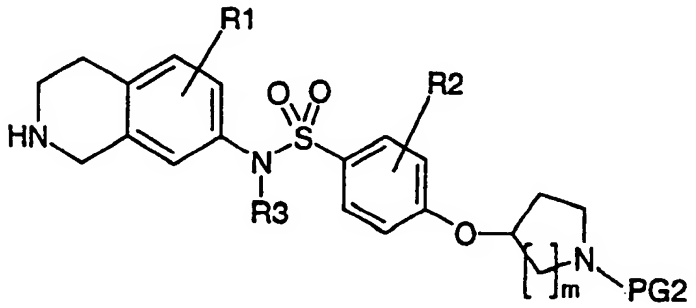
Compounds of the general formula XIV can be prepared by reacting, for example, a compound of the general formula XV



(XV)

in which R^1, R^2, R^3 and m have the meanings indicated and PG^2 is a protective group, such as, for example, the allyloxycarbonyl group, with a reagent removing the protective group. The protective group removal is carried out according to generally customary methods (see, for example, T.W. Green, P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley and Sons Inc. 1991), e.g. by means of palladium- or rhodium-catalysed cleavage.

Compounds of the general formula XV can be prepared by reacting, for example, a compound of the general formula XVI

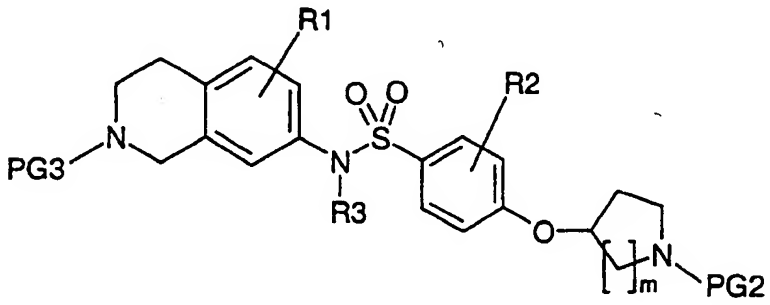


(XVI)

in which R^1, R^2, R^3, m and PG^2 have the meanings indicated above, with a guanylating reagent such as, for example, 1H-pyrazole-1-carboxamidine or S-methyl-

isothiourea in an inert solvent such as, for example, dimethylformamide, dioxane, dimethyl sulphoxide or toluene at temperatures between 0°C and the boiling point of the solvent, preferably at 0 to 30°C in the presence of an auxiliary base such as, for example, triethylamine, N-methylmorpholine, pyridine or ethyldiisopropylamine.

The compounds of the general formula XVI are prepared by reacting a compound of the general formula XVII

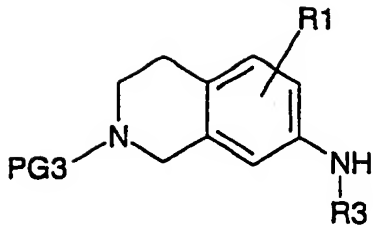


(XVII)

in which R^1, R^2, R^3, m and PG^2 have the meanings indicated above and PG^2 is not equal to PG^3, where PG^3 is a protective group such as, for example, the benzyloxycarbonyl group, the t-butyloxycarbonyl group or the allyloxycarbonyl group, with a reagent selectively removing the PG^2 protective group. The removal of the protective groups is carried out according to generally customary methods (see, for example, T.W. Green, P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley and Sons Inc. 1991), e.g. by acidic reagents such as hydrogen bromide in glacial acetic acid or trifluoroacetic acid or ethereal HCl solution or hydrogenolytically.

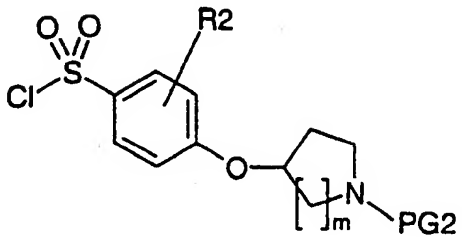
The compounds of the general formula XVII can be prepared from the appropriate precursors analogously to the compounds of the general formula IV.

Alternatively, the compounds of the general formula XVII can also be prepared by reacting a compound of the general formula XVIII



(XVIII)

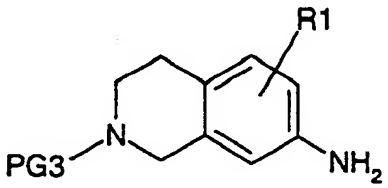
in which R^1, R^3 and PG^3 have the meanings indicated above, with a compound of the general formula XIX



(XIX)

in which R^2, m and PG^2 have the meanings indicated above. The reaction is carried out in an inert solvent such as N,N-dimethylformamide, N-methylpyrrolidone, dioxane, tetrahydrofuran, dichloromethane or toluene in the presence of a base such as, for example, sodium carbonate, potassium carbonate, 1,5-diazabicyclo-[5.4.0]undec-5-ene, triethylamine, N-methylmorpholine or ethyldiisopropylamine at temperatures between -20°C and the boiling point of the solvent, preferably between 0°C and 80°C.

The compounds of the general formula XVIII can be prepared from compounds of the general formula XX

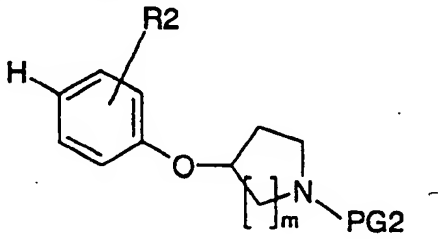


(XX)

in which R^1 and PG^3 have the meanings indicated above, by alkylation with compounds of the type R^3-Y, in which R^3 has the meaning indicated above and Y is halogen, tosylate, mesylate or triflate, in an inert solvent such as dioxane, tetrahydrofuran, N,N-dimethyl-formamide, N-methylpyrrolidone or toluene in the presence of a base such as, for example, sodium carbonate, potassium carbonate, 1,5-diazabicyclo-

[5.4.0]undec-5-ene or ethyldiisopropylamine at temperatures between 0°C and the boiling point of the solvent, preferably between room temperature and 80°C. Compounds of the type R^3-Y are either commercially available or are known from the literature or can be prepared from precursors which are commercially available or are known from the literature according to standard methods. Alternatively, the compounds of the general formula XVIII can also be obtained starting from compounds of the general formula XX, by reductive amination of the corresponding aldehyde. These reactions are carried out in an inert solvent such as dichloroethane, tetrahydrofuran, dioxane, ethanol, methanol or diglyme, in the presence of a reducing agent such as, for example, sodium borohydride, sodium cyanoborohydride or sodium triacetoxyborohydride, at temperatures between -20°C and the boiling point of the solvent, preferably between 0°C and 60°C. The corresponding aldehydes are either commercially available or are known from the literature or can be prepared according to standard methods from precursors which are commercially available or are known from the literature. The compounds of the general formula XX can be prepared from the corresponding precursors analogously to the compounds of the general formula XI.

The compounds of the general formula XIX can be prepared by sulphochlorinating a compound of the general formula XXI

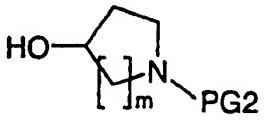


(XXI)

in which R^2, m and PG^2 have the meanings indicated above. This is carried out in an inert solvent such as dichloromethane, chloroform or carbon tetrachloride using a sulphochlorinating reagent such as

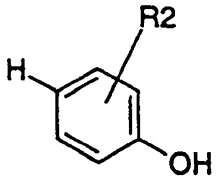
chlorosulphonic acid, if appropriate in the presence of thionyl chloride, sulphuryl chloride or phosphoryl chloride at temperatures between -20°C and the boiling point of the solvent, preferably between 0°C and 40°C.

The compounds of the general formula XXI are prepared by condensing a compound of the general formula XXII



(XXII)

in which PG^2 and m have the meanings indicated above, with a compound of the general formula XXIII



(XXIII)

in which R^2 has the meaning indicated above, in an inert solvent such as dioxane, tetrahydrofuran or toluene in the presence of diethyl azodicarboxylate and triphenylphosphine, trimethyl or triethyl phosphite at temperatures between 0 and 50°C, preferably at room temperature.

Compounds of the general formula XXII in which m and PG^2 have the meanings indicated above are either commercially available or are known from the literature or can be prepared according to processes known from the literature (see, for example, K.L. Bhat, D.M. Flanagan, M.M. Jouillé, *Synth. Commun.* **1985**, *15*, 587-598; P.G. Houghton, G.R. Humphrey, D.J. Kennedy, D.C. Roberts, S.H. Wright, *J. Chem. Soc. Perkin Trans. 1* **1993**, *13*, 1421-1424; T.W. Green, P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley and Sons Inc. 1991).

Compounds of the general formula XXIII in which R^2 has the meaning indicated are either commercially available or are known from the literature or can be prepared according to standard methods from precursors

which are commercially available or are known from the literature.

Certain compounds of the general formula I can subsequently be converted into other compounds of the general formula I.

This relates to compounds of the general formula I in which R^1, R^2, R^3, R^4, n and m have the meanings indicated above and one or more of the radicals R^1, R^2, R^3 is or comprises a methoxy group. By means of treatment with customary reagents removing the methyl group (see, for example, T.W. Green, P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley and Sons Inc. 1991) such as, for example, trimethylsilyl iodide or boron tribromide in an inert solvent such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride, tetrahydrofuran, dioxane, acetone, acetonitrile at temperatures between 0°C and the boiling point of the solvent, preferably between 0°C and 60°C, these compounds can be converted into the corresponding compounds of the general formula I having a free hydroxyl group.

This also relates to compounds of the general formula I in which R^1, R^2, R^3, R^4, n and m have the meanings indicated above and one or more of the radicals R^1, R^2 is or comprises an ethoxy- or methoxycarbonyl group. By means of acidic or alkaline hydrolysis in an inert solvent such as tetrahydrofuran, dioxane, acetone, ethanol, methanol or water at temperatures between 0°C and the boiling point of the solvent, preferably between room temperature and 60°C, these compounds can be converted into the corresponding compounds of the general formula I having a free carboxyl group.

This also relates to compounds of the general formula I in which R^1, R^2, R^3, R^4, n and m have the meanings indicated above and one or more of the radicals R^1, R^2 is a benzyloxy group. By means of catalytic hydrogenation in inert solvents such as, for

example, methanol, ethanol, tetrahydrofuran or dioxane in the presence of a catalyst, preferably palladium on carbon, the benzyl group is in this case replaced by a hydrogen atom (see, for example, T.W. Green, P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley and Sons Inc. 1991). The removal of the benzyl group is also carried out by reaction with a strong acid such as trifluoroacetic acid in the presence of mesitylene, anisole or thioanisole at temperatures between 0 and 50°C, preferably at room temperature, or by treatment with Lewis acids such as boron trifluoride etherate in an inert solvent such as toluene, acetonitrile, diethyl ether or tetrahydrofuran at temperatures between 0°C and the boiling point of the solvent, preferably between room temperature and the boiling point of the solvent.

This also relates to compounds of the general formula I in which R^1, R^2, R^3, R^4, n and m have the meanings indicated above and one or more of the radicals R^1, R^2 is an allyloxy group. By means of transition metal-catalysed cleavage, for example in the presence of a rhodium catalyst such as tris-triphenylphosphine-rhodium chloride or of a palladium catalyst such as tetrakis-triphenylphosphine-palladium in an inert solvent such as tetrahydrofuran or dioxane, if appropriate in the presence of a nucleophile such as, for example, diethyl malonate, tributyltin hydride, 5,5-dimethylcyclohexane-1,3-dione or piperidine at temperatures between 0°C and 50°C, preferably at room temperature, the allyl group is in this case replaced by a hydrogen atom (see, for example, T.W. Green, P.G.M. Wuts, "Protective Groups in Organic Synthesis", 2nd ed., John Wiley and Sons Inc. 1991).

Pure enantiomers of the compounds of the formula I are obtained either by resolution (via salt formation with optically active acids or bases) or by employing optically active starting substances in the synthesis or by enzymatically hydrolysing them.

Apart from the compounds mentioned in the examples, the following compounds are preferred within the meaning of the invention:

1. 7-{4-[1-(1-Iminoethyl)piperidin-4-yloxy]benzenesulphonylamino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine

2. 7-{4-[1-(1-Iminopropyl)piperidin-4-yloxy]benzenesulphonylamino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine

3. 7-{4-[1-(Cyclopropyliminomethyl)piperidin-4-yloxy]benzenesulphonylamino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine

4. 7-(4-{1-[Imino-(4-methoxyphenyl)methyl]piperidin-4-yloxy}benzenesulphonylamino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine

5. 7-{4-[1-(Iminothiophen-2-ylmethyl)piperidin-4-yloxy]benzenesulphonylamino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine

6. 7-{[4-(1-Carbamimidoylpiperidin-4-yloxy)benzenesulphonyl]methylamino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine

7. 7-({4-[1-(1-Iminoethyl)piperidin-4-yloxy]benzenesulphonyl}methylamino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine

8. 7-({4-[1-(1-Iminopropyl)piperidin-4-yloxy]-benzenesulphonyl}methylamino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

9. 7-({4-[1-(Cyclopropyliminoethyl)piperidin-4-yloxy]benzenesulphonyl}methylamino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

10. 7-[(4-{1-[Imino-(4-methoxyphenyl)methyl]piperidin-4-yloxy}benzenesulphonyl)methylamino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

11. 7-({4-[1-(Iminothiophen-2-ylmethyl)piperidin-4-yloxy]benzenesulphonyl}methylamino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

12. 7-{[4-(1-Carbamimidoylpiperidin-4-yloxy)benzenesulphonyl]ethylamino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine

13. 7-(Ethyl-{4-[1-(1-Iminoethyl)piperidin-4-yloxy]-benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

14. 7-(Ethyl-{4-[1-(1-Iminopropyl)piperidin-4-yloxy]-benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

15. 7-({4-[1-(Cyclopropyliminomethyl)piperidin-4-yloxy]benzenesulphonyl}ethylamino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

16. 7-[Ethyl-(4-{1-[Imino(4-methoxyphenyl)methyl]-piperidin-4-yloxy}benzenesulphonyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

17. 7-(Ethyl-{4-[1-(Iminothiophen-2-ylmethyl)-piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

18. 7-{[4-(1-Carbamimidoyl)piperidin-4-yloxy)benzenesulphonyl]cyclopropylamino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine

19. 7-(Cyclopropyl-{4-[1-(1-iminoethyl)piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

20. 7-(Cyclopropyl-{4-[1-(1-iminopropyl)piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

21. 7-(Cyclopropyl-{4-[1-(cyclopropyliminomethyl)-piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

22. 7-[Cyclopropyl-(4-{1-[Imino-(4-methoxyphenyl)-methyl]piperidin-4-yloxy}benzenesulphonyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

23. 7-(Cyclopropyl-{4-[1-(iminothiophen-2-ylmethyl)-piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

24. 7-{Allyl-[4-(1-carbamimidoylpiperidin-4-yloxy)-benzenesulphonyl]amino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine

25. 7-(Allyl-{4-[1-(1-iminoethyl)piperidin-4-yloxy]-benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

26. 7-(Allyl-{4-[1-(1-iminopropyl)piperidin-4-yloxy]-benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

27. 7-(Allyl-{4-[1-(cyclopropyliminomethyl)piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

28. 7-[Allyl-(4-{1-[imino-(4-methoxyphenyl)methyl]-piperidin-4-yloxy}benzenesulphonyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

29. 7-(Allyl-{4-[1-(iminothiophen-2-ylmethyl)-piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

30. 7-{Benzyl-[4-(1-carbamimidoylpiperidin-4-yloxy)-benzenesulphonyl]amino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine

31. 7-(Benzyl-{4-[1-(1-iminoethyl)piperidin-4-yloxy]-benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

32. 7-(Benzyl-{4-[1-(1-iminopropyl)piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

33. 7-(Benzyl-{4-[1-(cyclopropyliminomethyl)piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

34. 7-[Benzyl-(4-{1-[imino-(4-methoxyphenyl)methyl]-piperidin-4-yloxy}benzenesulphonyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

35. 7-(Benzyl-{4-[1-(iminothiophen-2-ylmethyl)-piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

36. 7-[[4-(1-Carbamimodoylpiperidin-4-yloxy)benzenesulphonyl]-(2-hydroxyethyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

37. 7-((2-Hydroxyethyl)-{4-[1-(1-iminoethyl)piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

38. 7-((2-Hydroxyethyl)-{4-[1-(1-iminopropyl)-piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

39. 7-[{4-[1-(Cyclopropyliminomethyl)piperidin-4-yloxy]benzenesulphonyl}-(2-hydroxyethyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

40. 7-[(2-Hydroxyethyl)-(4-{1-[imino-(4-methoxyphenyl)methyl]piperidin-4-yloxy}benzenesulphonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

41. 7-((2-Hydroxyethyl)-{4-[1-(iminothiophen-2-ylmethyl)piperidin-4-yloxy]benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

42. [[4-(1-Carbamimidoylpiperidin-4-yloxy)benzenesulphonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)amino]acetic acid

43. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(1-iminoethyl)piperidin-4-yloxy]-benzenesulphonyl}amino)acetic acid

44. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(1-iminopropyl)piperidin-4-yloxy]-benzenesulphonyl}amino)acetic acid

45. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(cyclopropyliminomethyl)piperidin-4-yloxy]benzenesulphonyl}amino)acetic acid

46. [(2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-(4-{1-[imino-(4-methoxyphenyl)methyl]-piperidin-4-yloxy}benzenesulphonyl)amino]acetic acid

47. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(iminothiophen-2-ylmethyl)piperidin-4-yloxy]benzenesulphonyl}amino)acetic acid

48. 4-[[4-(1-Carbamimidoylpiperidin-4-yloxy)benzenesulphonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)amino]butyric acid

49. 4-((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(1-iminoethyl)piperidin-4-yloxy]-benzenesulphonyl}amino)butyric acid

50. 4-((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(1-iminopropyl)piperidin-4-yloxy]-benzenesulphonyl}amino)butyric acid

51. 4-((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(cyclopropyliminomethyl)piperidin-4-yloxy]benzenesulphonyl}amino)butyric acid

52. 4-[(2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-(4-{1-[imino-(4-methoxyphenyl)methyl]-piperidin-4-yloxy}benzenesulphonyl)amino]butyric acid

53. 4-((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(iminothiophen-2-ylmethyl)piperidin-4-yloxy]benzenesulphonyl}amino)butyric acid

54. Ethyl [[4-(1-carbamimidoylpiperidin-4-yloxy)-benzenesulphonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)amino]acetate

55. Ethyl ((2-carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(1-iminoethyl)piperidin-4-yloxy]benzenesulphonyl}amino)acetate

56. Ethyl ((2-carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(1-iminopropyl)piperidin-4-yloxy]benzenesulphonyl}amino)acetate

57. Ethyl ((2-carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(cyclopropyliminomethyl)-piperidin-4-yloxy]benzenesulphonyl}amino)acetate

58. Ethyl [(2-carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-(4-{1-[imino-(4-methoxyphenyl)-methyl]piperidin-4-yloxy}benzenesulphonyl)-amino]acetate

59. Ethyl ((2-carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(iminothiophen-2-ylmethyl)-piperidin-4-yloxy]benzenesulphonyl}amino)acetate

60. 7-{Acetyl-[4-(1-carbamimidoylpiperidin-4-yloxy)-benzenesulphonyl]amino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine

61. 7-(Acetyl-{4-[1-(1-iminoethyl)piperidin-4-yloxy]-benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

62. 7-(Acetyl-{4-[1-(1-iminopropyl)piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

63. 7-(Acetyl-{4-[1-(cyclopropyliminomethyl)piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

64. 7-[Acetyl-(4-{1-[imino-(4-methoxyphenyl)methyl]-piperidin-4-yloxy}benzenesulphonyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

65. 7-(Acetyl-{4-[1-(iminothiophen-2-ylmethyl)-piperidin-4-yloxy]benzenesulphonyl}amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine

66. 7-[[4-(1-Carbamimidoylpiperidin-4-yloxy)benzene-sulphonyl]-(4-methoxybenzoyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

67. 7-[{4-[1-(1-Iminoethyl)piperidin-4-yloxy]benzene-sulphonyl}-(4-methoxybenzoyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

68. 7-[{4-[1-(1-Iminopropyl)piperidin-4-yloxy]-benzenesulphonyl}-(4-methoxybenzoyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

69. 7-[{4-[1-(Cyclopropyliminomethyl)piperidin-4-yloxy]benzenesulphonyl}-(4-methoxybenzoyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

70. 7-[(4-{1-[Imino-(4-methoxyphenyl)methyl]piperidin-4-yloxy}benzenesulphonyl)-(4-methoxybenzoyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

71. 7-[{4-[1-(Iminothiophen-2-ylmethyl)piperidin-4-yloxy]benzenesulphonyl}-(4-methoxybenzoyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

72. [[4-(1-Carbamimidoylpiperidin-4-yloxy)benzene-sulphonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)amino]sulphonylacetic acid

73. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(1-iminoethyl)piperidin-4-yloxy]-benzenesulphonyl}amino)sulphonylacetic acid

74. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(1-iminopropyl)piperidin-4-yloxy]-benzenesulphonyl}amino)sulphonylacetic acid

75. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(cyclopropyliminomethyl)piperidin-4-yloxy]benzenesulphonyl}amino)sulphonylacetic acid

76. [(2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-(4-{1-[imino-(4-methoxyphenyl)methyl]-piperidin-4-yloxy}benzenesulphonyl)amino]-sulphonylacetic acid

77. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(iminothiophen-2-ylmethyl)piperidin-4-yloxy]benzenesulphonyl}amino)sulphonylacetic acid

78. [[4-(1-Carbamimidoylpiperidin-4-yloxy)benzoyl-sulphonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)amino]methylboronic acid

79. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(1-iminoethyl)piperidin-4-yloxy]benzene-sulphonyl}amino)methylboronic acid

80. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(1-iminopropyl)piperidin-4-yloxy]-benzenesulphonyl}amino)methylboronic acid

81. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(cyclopropyliminomethyl)piperidin-4-yloxy]benzenesulphonyl}amino)methylboronic acid

82. [(2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-(4-{1-[imino-(4-methoxyphenyl)methyl]-piperidin-4-yloxy}benzenesulphonyl)amino]methyl-boronic acid

83. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(iminothiophen-2-ylmethyl)piperidin-4-yloxy]benzenesulphonyl}amino)methylboronic acid

84. 7-[4-(1-Carbamimidoylpyrrolidin-3-(S)-yloxy)-benzenesulphonylamino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine

85. [[4-(1-Carbamimidoylpyrrolidin-3-(S)-yloxy)-benzenesulphonylamino]-(2-carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)amino]sulphonylacetic acid

86. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(1-iminoethyl)pyrrolidin-3-(S)-yloxy]-benzenesulphonyl}amino)sulphonylacetic acid

87. [[4-(1-Carbamimidoylpyrrolidin-3-(S)-yloxy)-benzenesulphonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)amino]acetic acid

88. ((2-Carbamimidoyl-1,2,3,4-tetrahydroisoquinolin-7-yl)-{4-[1-(1-iminoethyl)pyrrolidin-3-(S)-yloxy]-benzenesulphonyl}amino)acetic acid

The following examples illustrate the invention, without restricting it thereto.

Example 1:

7-[4-(1-Carbamimidoylpiperidin-4-yloxy)benzene-sulphonylamino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine dihydrochloride

1. tert-Butyl 7-nitro-3,4-dihydro-1H-isoquinoline-2-carboxylate

A solution of 9.6 g (0.044 mol) of di-tert-butyl dicarbonate in 100 ml of methylene chloride is added dropwise at 5°C to a suspension of 8.6 g (0.040 mol) of 7-nitro-1,2,3,4-tetrahydro-isoquinoline hydrochloride (J.F. Ajao, C.W. Bird, *Heterocyclo. Chem.* **1985**, *22*, 239-331) and 16.6 ml

(0.170 mol) of triethylamine in 100 ml of methylene chloride. After stirring at room temperature for 24 hours, the resulting clear solution is successively extracted 3 × in each case with 50 ml each of water, 1 N acetic acid and saturated sodium bicarbonate solution. After drying and concentrating, the residue is triturated with isohexane, filtered off with suction and dried. 10.9 g (0.039 mol; 98%) of the title compound of m.p. 137-139°C are obtained as a brownish solid; EI-MS: 278 (M^+).

2. tert-Butyl 7-amino-3,4-dihydro-1H-isoquinoline-2-carboxylate

8.3 g (0.030 mol) of tert-butyl 7-nitro-3,4-dihydro-1H-isoquinoline-2-carboxylate are dissolved in 100 ml of ethyl acetate and hydrogenated in the presence of 1.0 g of palladium/carbon (10%) under normal pressure for 5 h at room temperature. After absorption of 2160 ml of hydrogen, the catalyst is removed by filtration and the solvent is stripped off. As a residue, 7.3 g (0.029 mol; 98%) of the title compound are obtained as a light brown solid of m.p. 75-77°C; EI-MS: 248 (M^+).

3. tert-Butyl 7-benzylamino-3,4-dihydro-1H-isoquinoline-2-carboxylate

A solution of 5.0 g (0.020 mol) of tert-butyl 7-amino-3,4-dihydro-1H-isoquinoline-2-carboxylate in 50 ml of methanol is treated with 2.40 ml (0.022 mol) of benzaldehyde and stirred at room temperature for 16 h. The resulting reaction mixture is cooled to 5°C and 0.76 g (0.021 mol) of sodium borohydride is added in portions. After stirring at room temperature for 24 hours, the methanol is removed by distillation and the solid

residue is triturated with water, filtered off with suction and dried. 5.80 g (86%) of the title compound are obtained as a white solid. M.p. 110°C; (+)-FAB-MS: 339 (MH^+).

4. tert-Butyl 7-[benzyl-(4-hydroxybenzenesulphonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxylate

A solution of 9.1 g (0.027 mol) of tert-butyl 7-benzylamino-3,4-dihydro-1H-isoquinoline-2-carboxylate in 150 ml of abs. pyridine is treated in portions at 5°C with 6.24 g (0.030 mol) of 4-hydroxybenzenesulphonyl chloride (R.W. Campbell, H.W. Hill, *J. Org. Chem.* **1973**, *38*, 1047) and stirred at room temperature for 16 h. The pyridine is distilled off and the residue is dissolved in 150 ml of ethyl acetate. It is extracted successively 2 × in each case with 50 ml each of water, 1 N acetic acid and saturated sodium bicarbonate solution, and the organic phase is dried over sodium sulphate. After concentrating, the residue is chromatographed on a silica gel column for purification (eluent: isohexane/ethyl acetate 8:2, 7:3, 6:4, 1:1). After concentrating the appropriate column fractions, 10.9 g (82%) of the title compound are obtained as a white, crystalline solid of m.p. 172-175°C EI-MS:495 (M^+).

5. tert-Butyl 7-{benzyl-[4-(1-tert-butoxycarbonyl-piperidin-4-yloxy)benzenesulphonyl]amino}-3,4-dihydro-1H-isoquinoline-2-carboxylate

A solution of 9.2 g (0.019 mol) of tert-butyl 7-[benzyl-(4-hydroxybenzenesulphonyl)amino]-3,4-dihydro-1H-isoquinoline-2-carboxylate, 4.1 g (0.021 mol) of tert-butyl 4-hydroxypiperidine-1-carboxylate (analogously to K.L. Bhat, D.M. Flanagan, M.M. Jouillé, *Synth. Commun.* **1985**,

15, 587-598) and 5.4 g (0.021 mol) of triphenylphosphine in 150 ml of tetrahydrofuran is treated at 5°C with 3.3 ml (0.021 mol) of diethyl azodicarboxylate and stirred at room temperature for 24 h. After concentrating, the residue is chromatographed on a silica gel column for purification (eluent: isohexane/ethyl acetate 9:1, 8:2, 7:3). After concentrating the appropriate column fractions, 9.0 g (71%) of the title compound are obtained as a white solid. M.p. 142-144°C; (+)-FAB-MS: 678 (MH^+).

6. tert-Butyl 7-{[4-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzenesulphonyl]amino}-3,4-dihydro-1H-isoquinoline-2-carboxylate

8.9 g of tert-butyl 7-{benzyl-[4-(1-tert-butoxycarbonylpiperidin-4-yloxy)benzenesulphonyl]-amino}-3,4-dihydro-1H-isoquinoline-2-carboxylate (0.013 mol) are dissolved in 250 ml of ethyl acetate and hydrogenated in the presence of 2.0 g of palladium/carbon (10%) under normal pressure for 10 d at room temperature. The catalyst is removed by filtration and the filtrate is concentrated. The residue is chromatographed on a silica gel column for purification (eluent: isohexane/ethyl acetate 9:1, 8:2, 7:3). After concentrating the appropriate column fractions, 5.3 g (69%) of the title compound are obtained as a colourless oil. (+)-FAB-MS: 588 (MH^+).

7. 4-(Piperidin-4-yloxy)-N-(1,2,3,4-tetrahydro-isoquinolin-7-yl)benzenesulphonamide dihydrochloride

A solution of 2.5 g (0.004 mol) of tert-butyl 7-{[4-(1-tert-butoxycarbonylpiperidin-4-yloxy)-benzenesulphonyl]amino}-3,4-dihydro-1H-isoquinoline-2-carboxylate in 50 ml of diethyl

ether is treated at 5°C with 50 ml of ethereal HCl solution and then stirred at 5°C for 5 h. The precipitated white solid is removed by filtration and dried: 1.9 g (0.0126 mmol; 70.1%); m.p. 107-109°C; EI-MS: 387 (M^+).

8. 7-[4-(1-carbamimidoylpiperidin-4-yloxy)-benzene-sulphonylamino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine dihydrochloride

A solution of 0.9 g (0.002 mol) of 4-(piperidin-4-yloxy)-N-(1,2,3,4-tetrahydroisoquinolin-7-yl-benzenesulphonamide dihydrochloride and 1.2 g (0.008 mol) of 1H-pyrazole-1-carboxamidine hydrochloride (ref.: M.S. Bernatowicz, Y. Wu, G.R. Matsueda, *J. Org. Chem.* **1992**, *57*, 2497-2502) in 2 ml of dimethylformamide is treated at 5°C with 4.2 ml of diisopropylethylamine. After stirring at room temperature for 24 hours, it is treated 4 × with 25 ml of diethyl ether each time and the ether is decanted off. The residue which remains is dissolved in 15 ml of water, adjusted to pH 3 using 2 N HCl and chromatographed (eluent: H_2O, pH 3; H_2O/CH_3OH 6:4, pH 3) by means of preparative HPLC (RP-18 column, 15-25µm). After concentrating the appropriate column fractions and drying in vacuo (10^{-2} torr), 0.8g (74%) of the title compound is obtained as a white solid of m.p. 150°C (dec.); (+)-FAB-MS: 472(MH^+).

Example 2:

Description of pharmacological test

Obtainment of plasma

Nine parts of fresh blood from healthy donors are mixed with one part of sodium citrate solution (0.11 mol/l) and centrifuged at about 3000 rpm for

10 minutes at room temperature. The plasma is removed by pipette and can be stored at room temperature for about 8 h.

Activated partial thromboplastin time (APTT)

100 µl of citrate plasma and 100 µl of APTT reagent (Diagnostica Stago/Boehringer, Mannheim GmbH; contains lyophilisate cephalin with microcrystalline kieselguhr activator) are incubated at 37°C for 3 minutes together with 10 µl of dimethyl sulphoxide (DMSO) or 10 µl of a solution of the active substance in DMSO in a ball coagulometer (KC10 from Amelung). With addition of 100 µl of 0.025 M calcium chloride solution, a stopclock is started and the time until the occurrence of clotting is determined. In the control measurements, the APTT is about 28-35 seconds and is prolonged by active substances. If no clotting occurred after 5 minutes during the measurements, the test was stopped (>300).

The measured APTT times in seconds are indicated as the difference from the control in Table 1. The concentrations of the active substances in the final volume was 1000 µM (APTT 1000), 100 µM (APTT 100), 10 µM (APTT 10), 1 µM (APTT 1).

Thrombin time

200 µl of citrate plasma are incubated at 37°C for 2 minutes in a ball coagulometer (KC10 from Amelung). 10µl of dimethyl sulphoxide (DMSO) or a solution of the active substance in DMSO are/is added to 190 µl of thrombin reagent whose temperature has previously been adjusted (Boehringer Mannheim GmbH; contains about 3 U/ml of equine thrombin and 0.0125 M Ca^{++}. With addition of this 200 µl of solution to the plasma, a

stopclock is started and the time until the occurrence of clotting is determined. In the control measurements, the thrombin time is about 24 seconds and is prolonged by active substances. If no clotting occurred after 5 minutes during the measurements, the test was stopped (>300).

The measured thrombin times in seconds are indicated as the difference from the control in Table 1. The concentrations of the active substances in the final volume were 500 µM (TT 500).

Inhibition constants

The kinetic measurements were carried out in 0.1 M phosphate buffer containing 0.2 M saline solution and 0.5% polyethylene glycol 6000 (preparation see below) at pH 7.5 and 25°C in polystyrene semimicro cuvettes in a total volume of 1 ml. The reactions were started by addition of enzyme to preincubated solutions, which either contained dimethyl sulphoxide (control) or solutions of the test substance in DMSO (inhibitor stock solutions: 10 mM in DMSO). The increase in the extinction at 405 nm as a result of the release of 4-nitroaniline from the substrate was monitored photometrically over a period of 12 minutes. Measured values (extinction vs time) were determined at an interval of 20 seconds and these data were stored by computer.

The procedure for the determination of the inhibition constants K_i was as follows: the velocities V_0 (change in extinction per second; measurements without inhibitor) and V_i (change in extinction per second; measurements with inhibitor) were determined by linear regression, only the measuring points at which the substrate

concentration decreased by less than 15% being taken into account. K_M and V_{max} were determined from a series of measurements (constant inhibitor concentration, variable substrate concentrations) by non-linear fit to the equation

$$V = \frac{V_{max} \times [S]}{[S] + K_M}$$

The K_i value was obtained from the complete series of measurements with 16 data sets (measurements at 4 different substrate concentrations and in each case 4 different inhibitor concentrations) by non-linear regression from the equation

$$V_i = \frac{V_{max} \times [S]}{K_M \times (1 + [I] / K_i) + [S]}$$

V_{max} being the maximum velocity in the absence of an inhibitor, K_M the Michaelis constant and [S] the substrate concentration.

The measured K_i values are indicated in [µM] in Table 1.

FXa:

Stock solution: 990 µl of phosphate buffer solution (preparation see below) are treated with 10 µl of human factor Xa (Boehringer Mannheim GmbH; 10 U; suspension) and stored on ice for at most 4 hours. For measurement, 850 µl of phosphate buffer are thermostated (25°C) with 100 µl of substrate [N-methoxycarbonyl-(D)-norleucyl-glycyl-(L)-arginine-4-nitroaniline acetate; Chromozym X; Boehringer Mannheim GmbH; substrate concentrations used 800, 600, 400 and 200 µM; K_M 400 µM] and 25 µl of inhibitor solution or 25 µl of DMSO (control) in a photometer. The reaction is started by addition of 25 µl of stock solution.

Thrombin:

Human α-thrombin (Sigma; 100 U; specific activity: 2000 NIH units/mg) is dissolved in 1 ml of water and stored at -18°C in portions of 20 µl. Stock solution: 1480 µl of phosphate buffer solution (preparation see below) are treated with 20 µl of the α-thrombin solution prepared as above and stored on ice for at most 4 hours. For measurement, 850 µl of phosphate buffer are thermostated (25°C) with 100 µl of substrate [H-(D)-Phe-Pip-Arg-4-nitroaniline dihydrochloride; S-2238; Kabi; substrate concentrations used 100, 50, 30 and 20 µM; K_M 4 µM) and 25 µl of inhibitor solution or 25 µl of DMSO (control) in a photometer. The reaction is started by addition of 25 µl of stock solution.

Trypsin:

10 mg of bovine pancreatic trypsin (Sigma) are dissolved in 100 ml of 1 mM hydrochloric acid and stored at 2-8°C in a refrigerator. Stock solution: 990 µl of 1 mM hydrochloric acid are treated with 10 µl of the trypsin solution prepared as above and stored on ice for at most 4 hours. For measurement, 850 µl of phosphate buffer are thermostated (25°C) with 100 µl of substrate [H-(D)-Phe-Pip-Arg-4-nitroaniline dihydrochloride; S-2238; Kabi; substrate concentrations used 100, 50, 30 and 20 µM; K_M 45 µM) and 25 µl of inhibitor solution or 25 µl of DMSO (control) in a photometer. The reaction is started by addition of 25 µl of stock solution.

Preparation of the 0.1 M phosphate buffer solution (pH 7.5, 0.2 M NaCl):

8.90 g of $Na_2HPO_4 \cdot 2\ H_2O$, 5.84 g of NaCl and 2.50 g of polyethylene glycol 6000 are dissolved in 400 ml of distilled water and made up to a

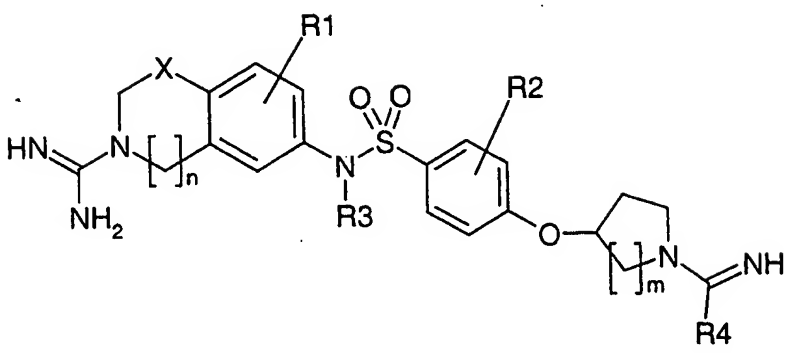
total volume of 500 ml with distilled water (solution I). 1.36 g of KH_2PO_4, 1.17 g of NaCl and 0.50 g of polyethylene glycol 6000 are dissolved in 80 ml of distilled water and made up to a total volume of 100 ml with distilled water (solution II). Sufficient solution II (about 85 ml) is then added to solution I until the pH is 7.5. The buffer solution is always freshly prepared (can be kept at 4°C for at most 10 days when stored in a refrigerator).

Table 1: Pharmacological data of Example Compound I

Example No.	K_i (fXa)	K_i (thrombin)	K_i (trypsin)	APTT 1000	APTT 100	APTT 10	APTT 1	TT 500
1	0.010	2	0.1	> 300	140	50	12	40

Claims

1. Compounds of general formula I



(I)

in which

R^1, R^2 independently of one another can be a hydrogen atom, a halogen atom, a hydroxyl group, an alkyl group, a cycloalkyl group, an alkenyl group, an alkynyl group, an aryl radical, a heteroaryl radical, an alkoxy group, an aralkyloxy group, an alkenyloxy group, an alkynyloxy group, a carboxyl group, an alkoxycarbonyl group, an alkenyloxycarbonyl group, an alkynyloxycarbonyl group, a hydroxyalkyl group, an alkoxyalkyl group, a carboxyalkyl group, an alkyloxycarbonylalkyl group, an alkenyloxycarbonylalkyl group or an alkynyloxycarbonylalkyl group;

R^3 can be a hydrogen atom, eine alkyl group, a cycloalkyl group, an alkenyl group, an alkynyl group, an aralkyl radical, a hydroxyalkyl group, an alkoxyalkyl group, an aminoalkyl group, a carboxyalkyl group, an alkyloxy-carbonylalkyl group, an alkenyloxycarbonylalkyl group or an alkynyloxycarbonylalkyl group, an alkylcarbonyl radical, an arylcarbonyl group, a carboxyalkylsulphonyl group, an alkyloxy-carbonylalkylsulphonyl group, a

dihydroxyborylalkyl group, a dialkoxyborylalkyl group or an optionally substituted 1,3,2-dioxaborolanylalkyl group or an optionally substituted 1,3,2-dioxaborinanylalkyl group;

R^4 is an optionally substituted amino group, an alkyl group, a cycloalkyl radical, an optionally substituted aryl radical or an optionally substituted heteroaryl radical;

X is a single bond, a carbonyl group, or an alkylene or an alkyleneoxy group;

n is the number 1 or 2 and

m is an integer between 1 and 4,

as well as hydrates, solvates and physiologically tolerable salts thereeof, optically active forms, racemates and diastereomer mixtures.

2. Compounds according to claim 1, in which

R^1, R^2 are identical or different and are a hydrogen atom, a fluorine atom, a chlorine atom, a hydroxyl group, a methyl group, an ethyl group, a methoxy group, a benzyloxy group, an allyloxy group, a carboxyl group, a methoxy- or ethoxycarbonyl group, a hydroxymethyl- or hydroxyethyl group or a carboxymethyl group;

R^3 is a hydrogen atom, a methyl group, an ethyl group, an isopropyl group, a cyclopropyl group, a cyclohexyl group, an allyl group, a propargyl group, a benzyl group, a hydroxyethyl group, a hydroxypropyl group, a methoxyethyl group, an aminoethyl group, a carboxymethyl group, a carboxyethyl group, a carboxypropyl group, an ethoxycarbonylmethyl group, an ethoxycarbonylethyl group, an ethoxy-carbonylpropyl group, an acetyl group, a 4-methoxybenzoyl group, a carboxymethylsulphonyl group, a carboxyethylsulphonyl group, a carboxypropylsulphonyl group, an

ethoxycarbonylmethylsulphonyl group, an ethoxycarbonylethylsulphonyl group, an ethoxycarbonylpropylsulphonyl group, a dihydroxyborylmethyl group, a dihydroxyborylpropyl group or a 4,4,5,5-tetramethyl-1,3,2-dioxaborolanylmethyl group;

R^4 is an amino group, a methyl group, an ethyl group, a cyclopropyl group, a cyclohexyl group, a 4-methoxyphenyl group or a thienyl group;

X is a methylene group;

n is the number 1 and

m can be the number 1 or 2.

3. The compounds according to claim 1, selected from

7-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzene-sulphonylamino}-3,4-dihydro-1H-isoquinoline-2-carbox-amidine,

7-{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzene-sulphonylamino}-3,4-dihydro-1H-isoquinoline-2-carbox-amidine,

7-{4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonylamino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonylamino)-3,4-dihydro-1H-iso-quinoline-2-carboxamidine,

7-{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonylamino}-3,4-dihydro-1H-iso-quinoline-2-carboxamidine,

7-{[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzene-sulphonyl]-methyl-amino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-({4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzene-sulphonyl}-methyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-({4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzene-sulphonyl}-methyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-({4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-methyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonyl)-methyl-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-({4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-methyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-{[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzene-sulphonyl]-ethyl-amino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(ethyl-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(ethyl-{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-({4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-ethyl-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[ethyl-(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(ethyl-{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-{[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzene-sulphonyl]-cyclopropyl-amino}-3,4-dihydro-1H-iso-quinoline-2-carboxamidine,

7-(cyclopropyl-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(cyclopropyl-{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(cyclopropyl-{4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[cyclopropyl-(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(cyclopropyl-{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-{allyl-[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzenesulphonyl]-amino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(allyl-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(allyl-{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(allyl-{4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[allyl-(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(allyl-{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-{benzyl-[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzenesulphonyl]-amino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(benzyl-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(benzyl-{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(benzyl-{4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[benzyl-(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(benzyl-{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzenesulphonyl]-(2-hydroxy-ethyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-((2-hydroxy-ethyl)-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-((2-hydroxy-ethyl)-{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[{4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-(2-hydroxy-ethyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[(2-hydroxy-ethyl)-(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-((2-hydroxy-ethyl)-{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

[[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzene-sulphonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amino]-acetic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzene-sulphonyl}-amino)- acetic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzene-sulphonyl}-amino)- acetic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)- acetic acid,

[(2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonyl)-amino]- acetic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)- acetic acid,

4-[[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzene-sulphonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydro-iso-quinolin-7-yl)-amino]-butyric acid,

4-((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzene-sulphonyl}-amino)- butyric acid,

4-((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzene-sulphonyl}-amino)- butyric acid,

4-((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)- butyric acid,

4-[(2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonyl)-amino]- butyric acid,

4-((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-butyric acid,

ethyl[[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzene-sulphonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydro-iso-quinolin-7-yl)-amino]-acetate,

ethyl ((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzene-sulphonyl}-amino)-acetate,

ethyl ((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-acetate,

ethyl ((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-acetate,

ethyl [(2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperi-din-4-yloxy}-benzenesulphonyl)-amino]-acetate,

ethyl ((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-acetate,

7-{acetyl-[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzenesulphonyl]-amino}-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(acetyl-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(acetyl-{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(acetyl-{4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[acetyl-(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-(acetyl-{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzenesulphonyl]-(4-methoxy-benzoyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzenesulphonyl}-(4-methoxy-benzoyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzenesulphonyl}-(4-methoxy-benzoyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[{4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-(4-methoxy-benzoyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonyl)-(4-methoxy-benzoyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

7-[{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-(4-methoxy-benzoyl)-amino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

[[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzenesulphonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amino]-sulphonylacetic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzene-sulphonyl}-amino)-sulphonylacetic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzene-sulphonyl}-amino)-sulphonylacetic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-sulphonylacetic acid,

[(2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonyl)-amino]-sulphonylacetic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-sulphonylacetic acid,

[[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzenesul-phonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydro-isoquino-lin-7-yl)-amino]-methylboronic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(1-imino-ethyl)-piperidin-4-yloxy]-benzenesul-phonyl}-amino)-methylboronic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(1-imino-propyl)-piperidin-4-yloxy]-benzenesul-phonyl}-amino)-methylboronic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(cyclopropyl-imino-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-methylboronic acid,

[(2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-(4-{1-[imino-(4-methoxy-phenyl)-methyl]-piperidin-4-yloxy}-benzenesulphonyl)-amino]-methylboronic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(imino-thiophen-2-yl-methyl)-piperidin-4-yloxy]-benzenesulphonyl}-amino)-methylboronic acid,

7-[4-(1-carbamimidoyl-pyrrolidin-3-(S)-yloxy)-benzene-sulphonylamino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine,

[[4-(1-carbamimidoyl-pyrrolidin-3-(S)-yloxy)-benzene-sulphonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amino]-sulphonylacetic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(1-imino-ethyl)-pyrrolidin-3-(S)-yloxy]-benzene-sulphonyl}-amino)-sulphonylacetic acid,

[[4-(1-carbamimidoyl-pyrrolidin-3-(S)-yloxy)-benzene-sulphonyl]-(2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-amino]-acetic acid,

((2-carbamimidoyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-{4-[1-(1-imino-ethyl)-pyrrolidin-3-(S)-yloxy]-benzene-sulphonyl}-amino)-acetic acid and

7-[4-(1-carbamimidoyl-piperidin-4-yloxy)-benzenesulphonylamino]-3,4-dihydro-1H-isoquinoline-2-carboxamidine dihydrochloride.

4. Compounds according to any one of claims 1-3 for the prevention and treatment of diseases such as thrombosis, apoplexy, cardiac infarct, inflammation and arteriosclerosis.

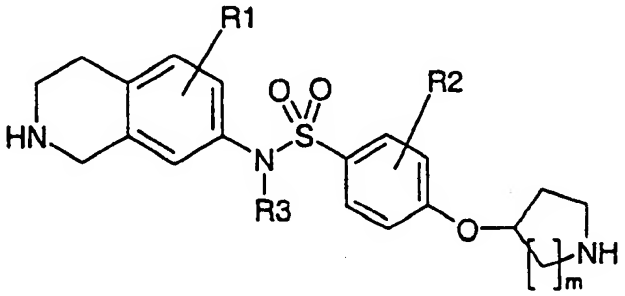
5. Pharmaceutical preparations, containing at least one compound according to any one of claims 1-3 in addition to usual carriers and adjuvants.

6. Use of compounds according to any one of claims 1-3 for the production of medicaments with antithromboembolic activity.

7. Method for the prevention and treatment of diseases such as thrombosis, apoplexy, cardiac infarct, inflammation and arteriosclerosis, which comprises the

administration of an effective amount of a compound according to any one of claims 1-3.

8. Process for the preparation of compounds of the formula I, which comprises the reaction of a compound of the formula III



(III)

in which R^1, R^2, R^3 and m have the meanings indicated in claim 1,
with a guanylating reagent in an inert solvent in the presence of an auxiliary base.

9. Process according to claim 8, in which 1H-pyrazole-1-carboxamidine or an S-alkylisothiourea is used as the guanylating reagent.

10. Process according to claim 8 or claim 9, in which dimethylformamide, dioxan, dimethyl sulphoxide or toluene is used as the solvent.

11. Process according to any one of claims 8-10, in which triethylamine, N-methylmorpholine, pyridine or ethyldiisopropylamine is used as the auxiliary base.

12. The compounds according to claims 1-3 when prepared according to a process of claims 8-11.

13. The compounds, use, methods and process as described above.

INTERNATIONAL SEARCH REPORT

Int· tional Application No
PCT/EP 99/00914

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D401/12 C07D409/14 A61K31/47

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE 195 30 996 A (BOEHRINGER MANNHEIM GMBH) 27 February 1997 see page 2, line 35; claim 1	1,4-7
A	EP 0 798 295 A (YAMANOUCHI PHARMA CO LTD) 1 October 1997 see abstract; claim 1 & WO 96 16940 A cited in the application	1,4-7
A	EP 0 528 369 A (THOMAE GMBH DR K) 24 February 1993 * Beispiel 11 (2) und 11 (3)	1,4-7
A	EP 0 540 051 A (DAIICHI SEIYAKU CO) 5 May 1993 cited in the application see abstract	1,4-7

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 June 1999	24/06/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

.rnational application No.
PCT/EP 99/00914

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 7
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 7 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Intr ional Application No
PCT/EP 99/00914

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